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Association between the *HLA-DQA1* rs2187668 polymorphism and risk of idiopathic membranous nephropathy

A PRISMA-compliant meta-analysis

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Abstract

Objective: Numerous studies have evaluated the association between the rs2187668 polymorphism in the human leucocyte antigen (HLA) complex class II HLA-DQ a-chain 1 (*HLA-DQA1*) gene and idiopathic membranous nephropathy (iMN) risk, which provided new insight into potential new targets for the treatment of iMN. However, this relationship remains inconclusive. Our aim was to evaluate the relationship between this polymorphism and iMN susceptibility by performing a meta-analysis.

Methods: Articles were identified in the PubMed, Google Scholar, EMBASE, Cochran Library databases. Meta-analyses were performed for rs2187668 allele frequency, genotypes, and the association with iMN susceptibility. Subgroup analyses, publication bias and sensitivity analyses were also conducted.

Results: 11 eligible studies (3209 cases and 7358 controls) from 7 articles were included. Statistical analyses were carried out using Stata 12.0, combining data from all the relevant studies. The pooled odds ratios (ORs) regarding the association between the *HLA-DQA1* rs2187668 polymorphism and iMN risk were statistically significant [A vs G: OR = 3.34, 95% confidence interval (CI) = 2.70–4.13; AA vs GA + GG: OR = 8.69, 95% CI = 6.64–11.36; GG vs GA + AA: OR = 0.25, 95% CI = 0.19–0.33;AA vs GG: OR = 12.61, 95% CI = 8.02–19.81; GA vs GG: OR = 3.45, 95% CI = 2.79–4.25].

Conclusions: Our pooled analysis showed a significant association between rs2187668—(A) allele and iMN susceptibility, and the intervention of this mutation might bring new therapeutic strategy for iMN. However, further studies should be performed to confirm this finding.

Abbreviations: CI = confidence interval, HLA-DQA1 = human leucocyte antigen-DQ a-chain 1, HWE = Hardy–Weinberg equilibrium, Ig = immunoglobulin, iMN/IMN = idiopathic membranous nephropathy, MHC = major histocompatibility complex, NOS = Newcastle–Ottawa Scale, ORs = odds ratios, PLA2R = phospholipase A2 receptor.

Keywords: gene polymorphism, *HLA-DQA1*, idiopathic membranous nephropathy, meta-analysis, rs2187668

1. Introduction

Idiopathic membranous nephropathy (iMN), one of the most common cause of nephrotic syndrome in the adult population, is a kidney-specific, autoimmune glomerular disease that presents with increased protein in the urine. It is now recognized that iMN is characterized by subepithelial immune deposits that consist immunoglobulin (Ig)G and complement.[1,2] Many studies demonstrated that the major target antigen of autoantibodies in iMN is an M-type phospholipase A2 receptor (PLA2R).[3,4] However, little is known about the therapeutic strategies of iMN. In recent years, numerous studies have indicated that certain genetic polymorphisms associated with susceptibility to this disease.[5,6] And this discovery has opened a new horizon in the therapy of iMN.

PLA2R, a major target antigen in iMN, are detectable in about 70% of patients from various ethnic groups.[7] Epitopes of PLA2R must be presented by the human leucocyte antigen (HLA)-encoded major histocompatibility complex (MHC) class II molecules to stimulate autoantibody production.[8] Therefore, HLA plays a critical role in the pathogenesis of iMN. The HLA region resides on chromosome 6p21.3, and this region is one of the most polymorphic regions of the genome in humans. human leucocyte antigen -DQ a-chain 1 (*HLA-DQA1)*, belonging to the group of HLA Class II regions, is part of the heterodimer anchored in the membrane, forming the antigen-binding groove. *HLA-DQA1* plays a central role in the immune system by presenting peptides derived from extracellular proteins to immunocompetent cells. Genome-wide association study (GWAS) identified risk alleles at *HLA* and *PLA2R* loci in European populations, with the top variant rs2187668 within

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Table 1

Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Ethnicity control type	Method	Cases	Controls	Cases				Controls			HWE	Quality
								GG	GA	AA	GG	GA	AA		
Kaga[11]	2017	Japanese	Asian	HB	PCR	58	50	51	0	70	49	1	0	0.94	8 (4,2,2)*
Bullich[12]	2014	Spanish	European	PB	PCR	89	286	40	47	2	215	65	6	0.68	8 (4,2,2)*
Lv[14]	2013	Chinese	Asian	PB	NR	1112	1020	853	248	11	912	106	2	0.55	8 (4,2,2)*
Ramachandran[15]	2015	Indian	Asian	PB	PCR	94	95	31	47	16	72	23	0	0.18	8 (4,2,2)*
Stanescu[9]	2011	French	European	PB	Illumina	75	157	36	32	7	129	26	2	0.60	7 (3,2,2)*
Stanescu[9]	2011	Dutch	European	PB	Illumina	146	1832	58	68	20	1371	428	33	0.95	7 (3,2,2)*
Stanescu[9]	2011	British	European	PB	Illumina	335	349	113	163	59	271	73	5	0.97	7 (3,2,2)*
Stanescu[9]	2011	Caucasian	Caucasian	NR	Illumina	556	2338	206	265	85	1771	528	39	0.96	7 (3,2,2)*
Qin[10]	2017	Chinese	Asian	PB	PCR	349	676	278	71	0	602	74	0	0.13	8 (4,2,2)*
Saeed[13]	2014	Amercian	Amercian	NR	NR	115	218	74	37	4	177	39	2	0.93	6 (2,2,2)*
Saeed[13]	2014	Caucasian	Caucasian	NR	NR	280	337	88	138	54	216	108	13	0.91	6 (2,2,2)*

HB = hospital-based, PB = population-based, NR = not reported, HWE = Hardy–Weinberg equilibrium, Quality was evaluated according to NOS.
* the final scores (the scores of the SELECTION, the scores of the COMPARABILITY, the scores of the OUTCOME AND EXPOSURE).

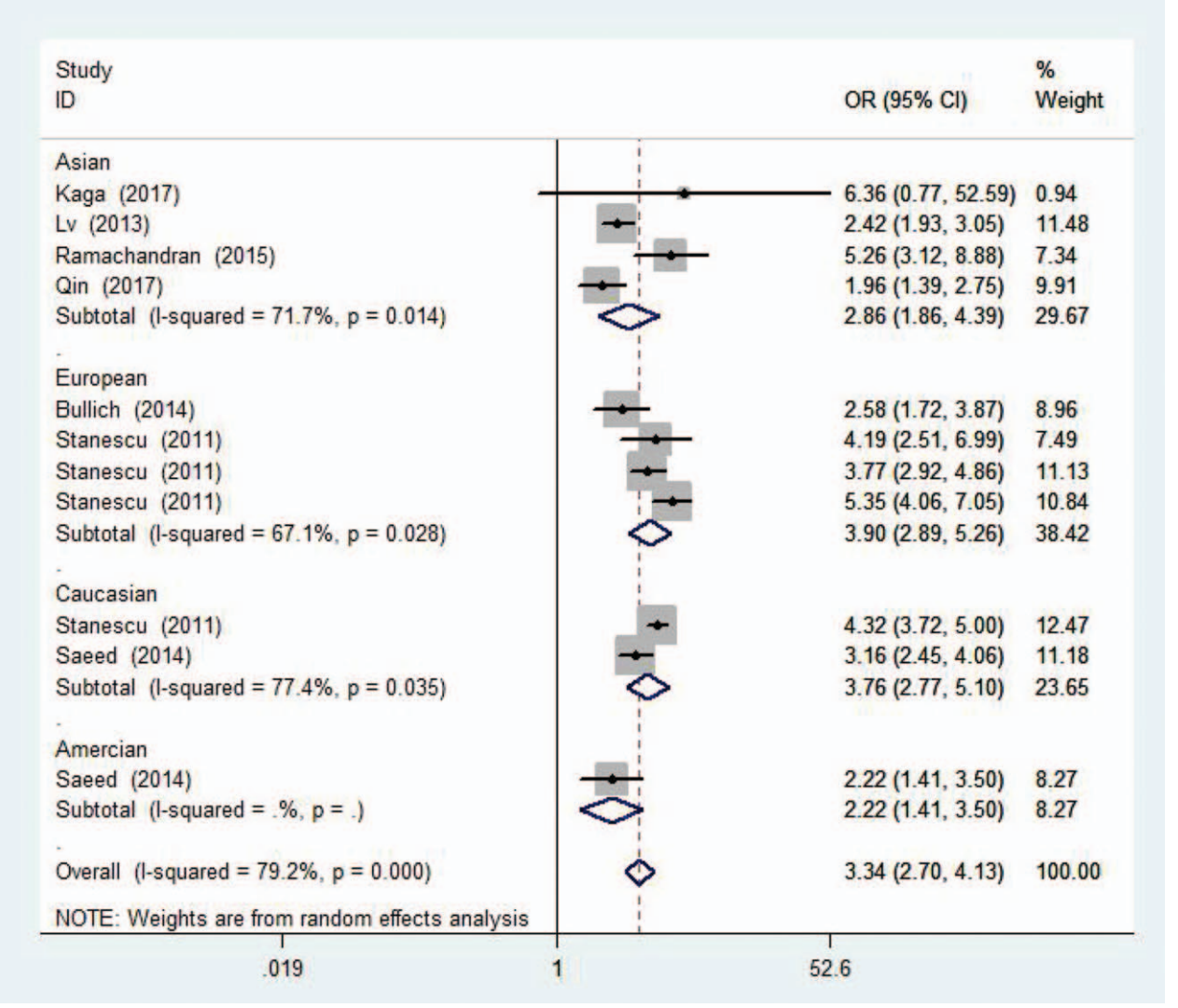

Figure 1. Meta-analysis for the OR of iMN associated with *HLA-DQA1* rs2187668 polymorphism (A vs G). iMN = idiopathic membranous nephropathy, OR = odds ratios.

Table 2

Summary of pooled ORs in the stratified analysis association between *HLA-DQA1* rs2187668 and iMN risk.

	N	A vs G		AA vs (GA+GG)		GG vs (GA+AA)		AA vs GG		GA vs GG	
		OR	P_h	OR	P_h	OR	P_h	OR	P_h	OR	P_h
Total	11	3.34 [2.70, 4.13]	<0.01	8.69 [6.64,11.36]	0.129	0.25 [0.19, 0.33]	<0.01	12.61 [8.02, 19.81]	0.056	3.45[2.79, 4.25]	<0.01
Ethnicity											
Asian	4	2.86 [1.86, 4.39]	0.014	10.90 [3.04, 39.07]	0.180	0.33 [0.21, 0.51]	0.020	16.12 [1.24, 208.98]	0.104	2.69 [1.94, 3.73]	0.134
European	4	3.90 [2.90, 5.26]	0.028	8.86 [5.54, 14.17]	0.052	0.20 [0.15, 0.26]	0.179	1.24 [0.77, 2.00]	0.038	4.38 [3.54, 5.43]	0.543
Caucasian	2	3.76 [2.77, 5.10]	0.035	8.63 [6.13, 12.16]	0.119	0.21 [0.16, 0.29]	0.119	14.59 [8.00, 26.59]	0.113	3.80 [2.80, 5.17]	0.126
America	1	2.22 [1.41, 3.50]	—	3.89 [0.70, 21.58]	—	0.42 [0.25,0.70]	—	4.78 [0.86, 26.69]	—	2.27 [1.34, 8.34]	—
control source											
PB	7	3.36 [2.49, 4.54]	<0.01	9.21 [5.89, 14.39]	0.092	0.25 [0.17, 0.36]	<0.01	11.98 [5.46, 26.29]	0.049	3.51 [2.62, 4.69]	0.002
HB	1	6.36 [0.77, 52.59]	—	—	—	0.15 [0.02, 1.25]	<0.01	—	—	6.73 [0.80, 56.69]	—
NR	3	3.28 [2.33, 4.63]	<0.01	8.36 [6.64,11.36]	0.189	0.26 [0.17, 0.39]	0.010	12.80 [6.86, 23.91]	0.114	3.33 [2.34, 4.74]	0.043

P_h = P value for heterogeneity, HB = hospital-based, PB = population-based, NR = not reported.

*HLA-DQA*1 showing higher risk effect compared with the top variant rs4664308 within *PLA2R1*.[9] Recent years, more and more published papers have revealed that the rs2187668 G > A polymorphism of *HLA-DQA1* was associated with iMN.[9–15]

Considering the relatively small sample size in most studies, it is possible to perform a quantitative synthesis of the evidence with rigorous methods. Meta-analysis has been proven to be an effective statistical method combining available studies to

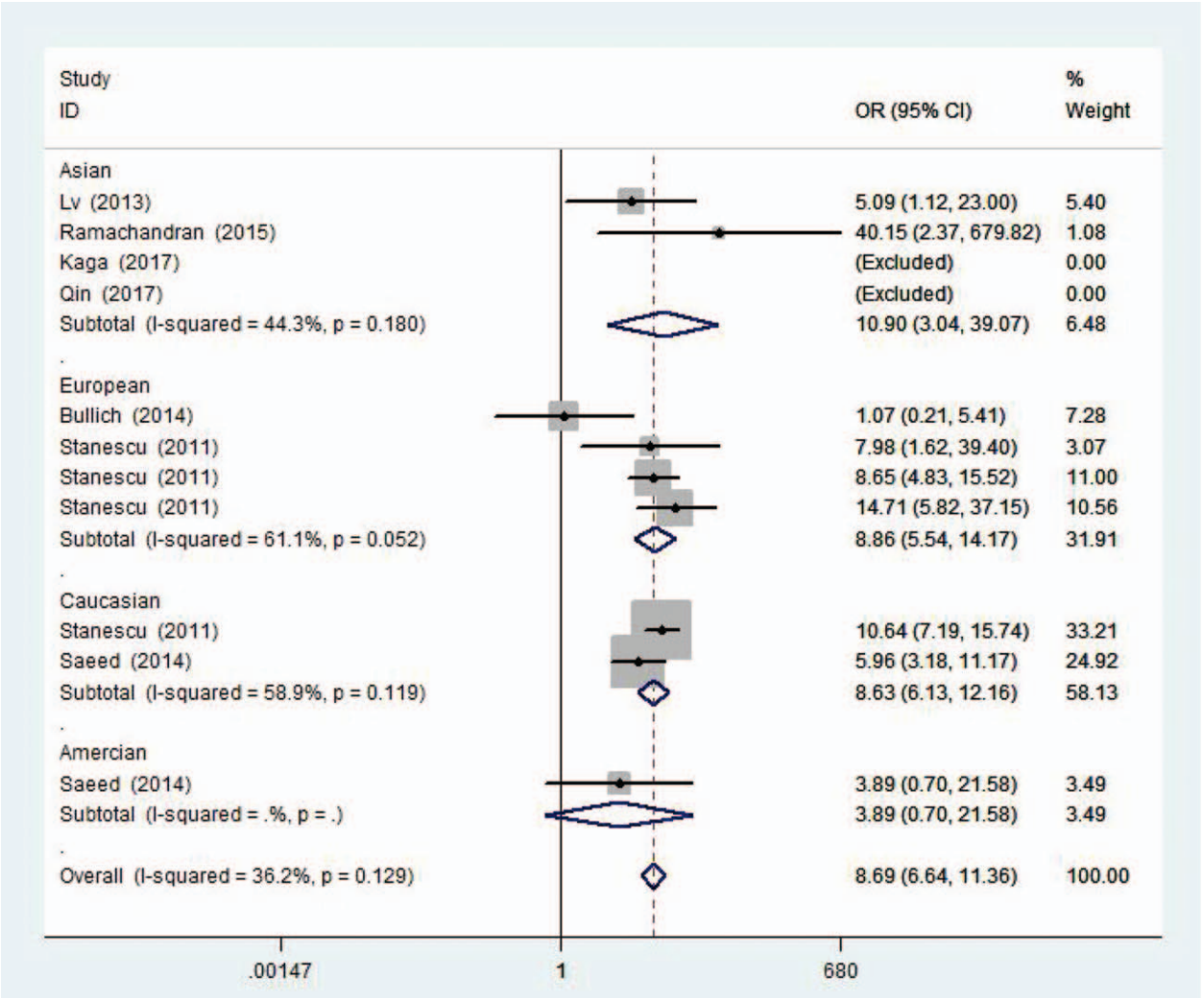

Figure 2. Meta-analysis for the OR of iMN associated with *HLA-DQA1* rs2187668 polymorphism (AA vs GA + GG). iMN = idiopathic membranous nephropathy, OR = odds ratios.

produce a precise conclusion. Therefore, we performed a meta-analysis on 11 published case and control studies to identify the precise association between *HLA-DQA1* rs2187668 G/A polymorphism and iMN risk.

2. Materials and methods

2.1. Selection of studies

Medical Subject Headings (MeSH) terms ("HLA-DQ alpha-chains" or "HLA-DQ a-chain 1" or "HLA-DQA1" or "rs2187668") and ("membranous nephropathy" or "membranous glomerulonephritis" or "idiopathic membranous nephropathy" or "MN" "iMN" or "IMN") were used in PubMed. These keywords retrieval strategies were also used in other databases (Google Scholar, Embase, Cochrane Library) for entries until April 2018. References of the retrieved publications were also reviewed. All eligible studies were retrieved, and their bibliographies were checked for any additional relevant and potential eligible studies.

2.2. Inclusion and exclusion criteria

Literatures fulfilled the following criteria:

(1) published in English;
(2) experimental subjects were diagnosed as iMN by renal biopsy;
(3) evaluated *HLA-DQA1* gene polymorphism rs2187668 and risk of iMN;
(4) were cohort-based or case-control;
(5) included sufficient data for calculating an odds ratio (OR) with 95% confidence interval (CI);
(6) case control groups genotype conformed to the Hardy–Weinberg (H–W) balance. If such data were unavailable, we attempted to contact the corresponding author to provide the missing data before the study was excluded. The major exclusion criteria included: review articles, meeting abstract, case reports, editorials, treatment outcome studies,meta-analysis were excluded; lack of sufficient data for calculation of ORs with 95% CIs; and when there were multiple

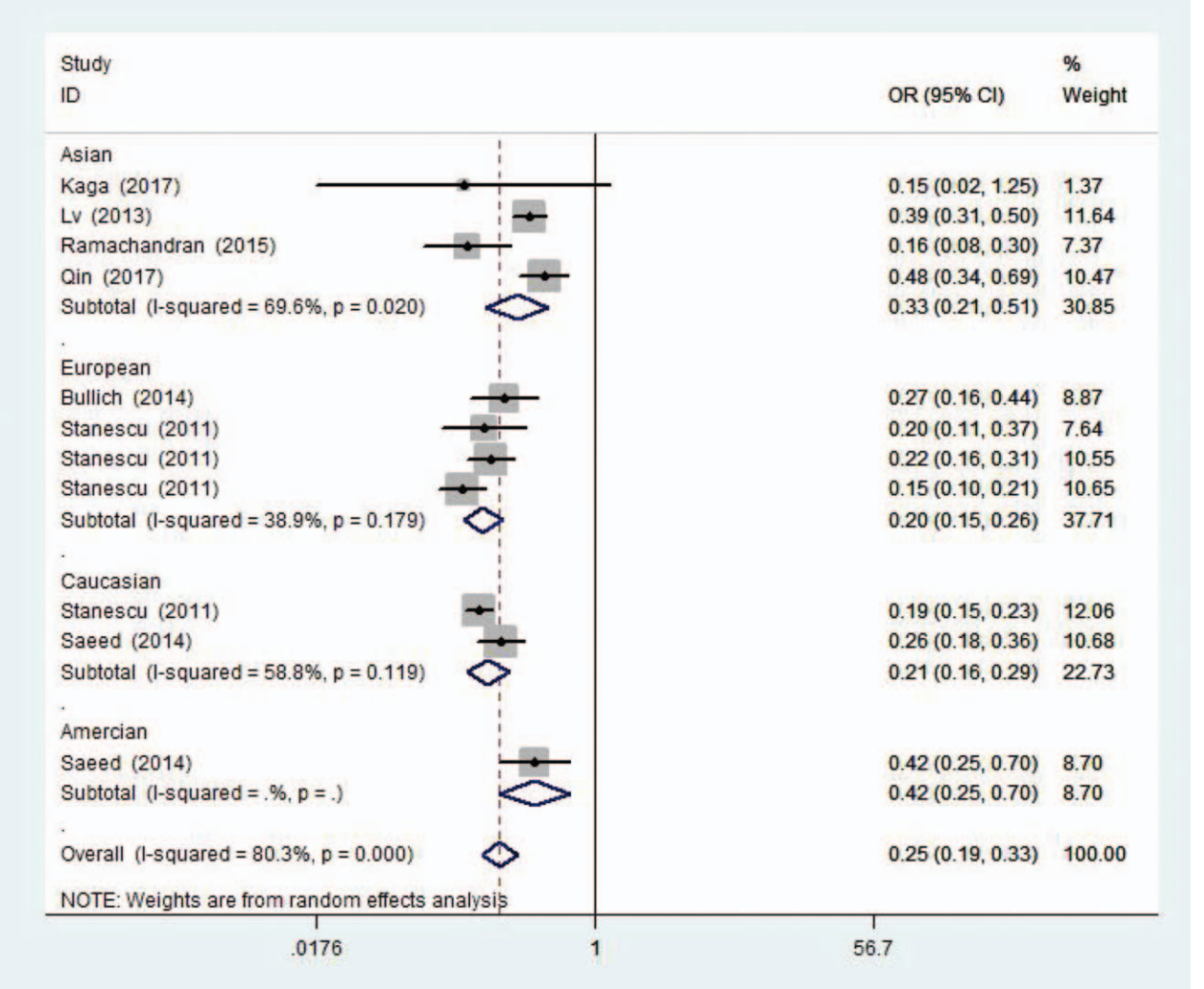

Figure 3. Meta-analysis for the OR of iMN associated with *HLA-DQA1* rs2187668 polymorphism (GG vs GA + AA). iMN = idiopathic membranous nephropathy, OR = odds ratios.

publications from the same study, only the largest population study was adopted, others were excluded.

2.3. Data extraction and synthesis

We performed this meta-analysis based on published studies. So there is no need to conduct special ethic review, and the ethical approval is not necessary. To exclude irrelevant and overlapping studies, two independent investigators (Liping Bao and Jushuang Li) examined the articles by using a standardized data extraction form. If genotype distributions were not given in the study, we calculated them from allele frequencies and number of cases and controls if the reported study was in accordance with Hardy–Weinberg equilibrium (HWE). Disagreements were resolved by discussion and consensus. If discussion and consensus were not achieved, the third reviewer (Shuang Hu) would make an ultimate decision. We extracted the following information from each study: first author, year of publication, ethnicity, and the number of cases and controls for each genotype, gene detection method, source of control groups, and statement of HWE.

2.4. Statistical analysis

The OR with 95% CI was used to assess the strength of association between *HLA-DQA1* rs2187668 G/A polymorphisms and iMN risk in 5 genetic models (A vs G, AA vs GA + GG, GG vs GA + AA, GG vs AA and GA vs GG). The *HLA-DQA1* rs2187668 polymorphism distribution in the control group was tested for HWE using the Pearson chi-square test.[16] Newcastle–Ottawa Scale (NOS) was used to access the quality of the inclusive studies. Cochran's chi-square-based Q-test and I^2 [2]test were performed to assess the between-study heterogeneity of studies. If the heterogeneity was not significant ($P > .1$, $I^2 < 50.0\%$), the fixed-effect model can be used to pool ORs; otherwise, the random-effect model was used. Subgroup analyses were performed based on variables, such as ethnicities and control tipies. Sensitivity analysis was conducted by deletion of a single study, in turn to, identify the influence of the individual data on pooled results and test the reliability of results. Begg funnel plots and Egger tests were used to access the potential publication bias. A 2-sided *P* value of less than .05 was considered statistical significant. All statistical analyses were conducted by Stata version 12.0 (StataCorp LP, College Station, TX).

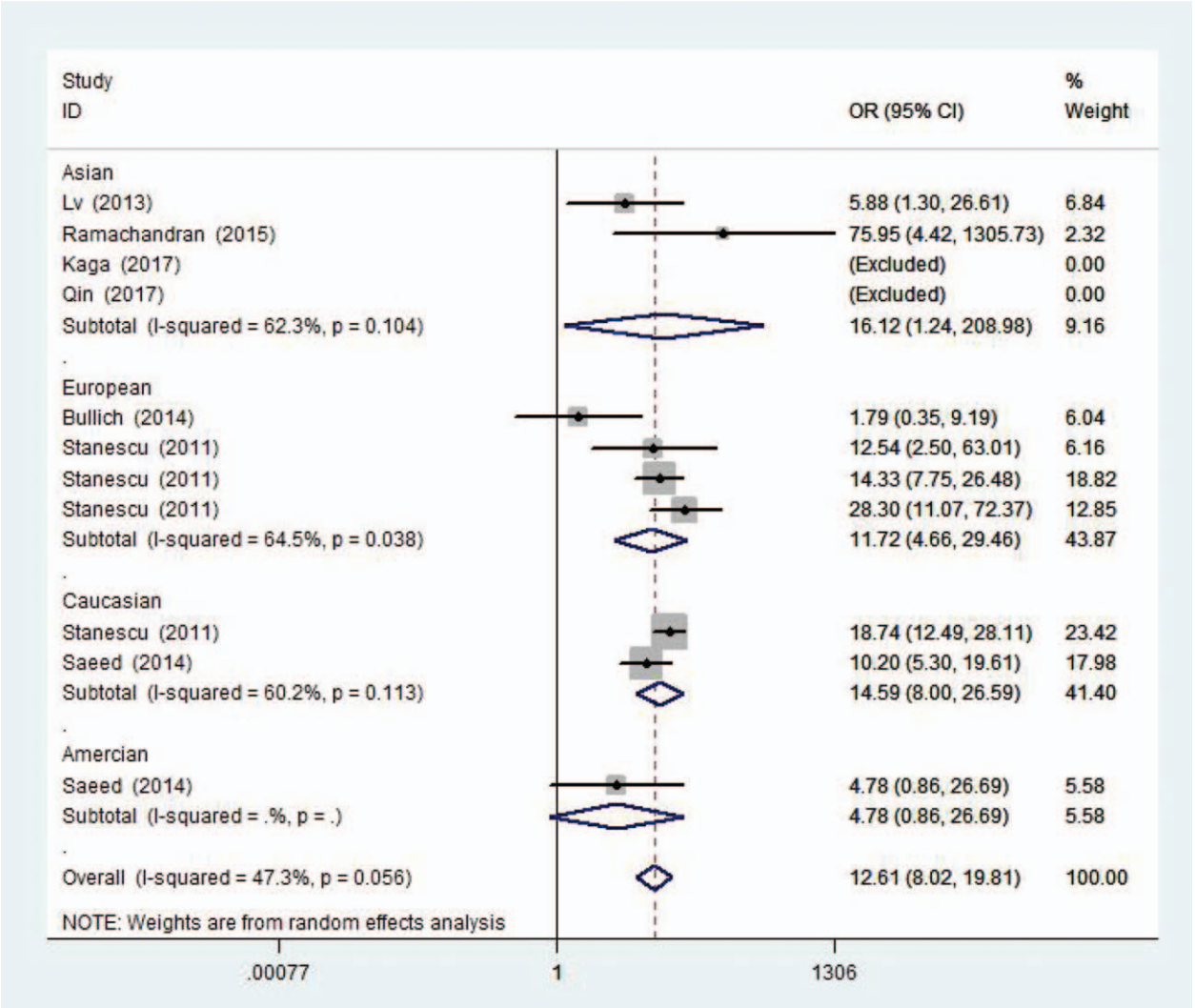

Figure 4. Meta-analysis for the OR of iMN associated with *HLA-DQA1* rs2187668 polymorphism (AA vs GG). iMN = idiopathic membranous nephropathy, OR = odds ratios.

3. Results

3.1. Study characteristics

A total of 36 potentially relevant citations were identified from databases. After we screened the titles and abstracts, 26 citations were removed due to irrelevant topics (not about iMN and *HLA-DQA1* rs2187668 polymorphism). Then, the full-text of the rest of 10 citations were downloaded for reading carefully; we removed 3 citations due to insufficient genotype data for extraction. All 11 case and control studies from 7 articles were included in our meta-analysis, incorporating 3209 iMN cases and 7358 controls. The populations were from Europe (France, Britain, Netherlands and Spain), Asia (Japan, India and China), Caucasus and America. The characteristics of these studies and the quality scores were presented in Table 1.

3.2. Main results

The evaluation of association between *HLA-DQA1* rs2187668 G/A polymorphism and iMN risk was presented in Table 2.

Overall, there was correlation between the susceptibility of *HLA-DQA1* gene and iMN, and the difference has statistical significance (A vs G: OR = 3.34, 95% CI = 2.70-4.13; AA vs GA + GG: OR = 8.69, 95%CI = 6.64–11.36; GG vs GA + AA: OR = 0.25, 95% CI = 0.19–0.33;AA vs GG: OR = 12.61, 95% CI = 8.02–19.81; GA vs GG: OR = 3.45, 95% CI = 2.79–4.25, respectively). In order to identify potential differences based on ethnicity, subgroup analysis was performed. Since only one study was performed in an American population, however, it should be noted that the ethnicity-based analysis may not be reliable in regard to the American subgroup. The results suggested the *HLA-DQA1* rs2187668 G/A gene has a certain correlation with iMN susceptibility among Asian, European and Caucasian subjects. As shown in Figures 1–5.

3.3. Sensitivity analysis

Sensitivity analysis was performed by omitting each study in turn to estimate the influence of individual study on the pooled OR (Fig. 6). The result of sensitivity analysis showed that the corresponding pooled OR and principal results did not change appreciably, suggesting stability of the meta-analyses.

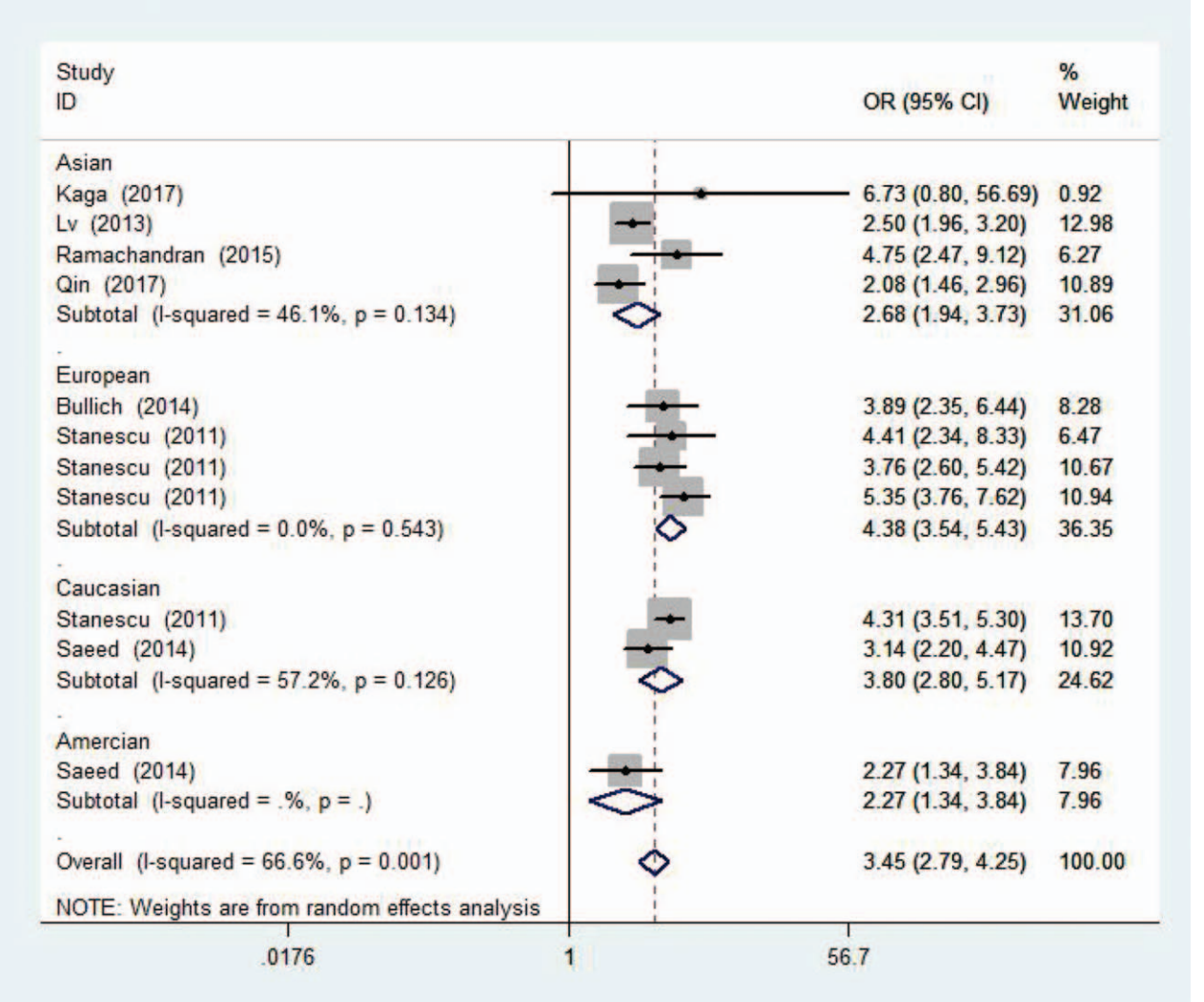

Figure 5. Meta-analysis for the OR of iMN associated with *HLA-DQA1* rs2187668 polymorphism (GA vs GG). iMN = idiopathic membranous nephropathy, OR = odds ratios.

3.4. Publication bias

Begg funnel plots and Egger test were generated to detect the potential publication bias in the literature used. The result did not show any evidence of publication bias based on Begg funnel plot ($P_{Begg}=1$, A vs G, Fig. 7) or Egger regression test ($P_{Egger}=0.523$, A versus G). Similarly, no publication bias for the association between *HLA-DQA1* rs2187668 polymorphism and iMN susceptibility under the other genetic models.

4. Discussions

iMN, is an autoimmune disease that represents approximately 80% of MN cases, in which circulating antibodies to a conformation-dependent epitope on the target antigen.[17] The autoimmune response is regulated by genes at the *HLA-DQA1* locus.[18] Therapies for iMN that include the use of immunosuppressive drugs and nonspecific antiproteinuric measures have led to disappointing results, which prompted increased interest in the discovery of new therapeutic targets.[19] A variety of studies have focused on the association between the *HLA-DQA1* gene rs2187668 polymorphism and iMN.[9–15] And recent studies indicated that *HLA-DQA1* gene rs2187668 may confer susceptibility to iMN by presenting T cell epitopes on *PLA2R*.[20] However, the results obtained from such investigations have been inconclusive. To derive a more precise estimation of the relationship, we performed this meta-analysis, combining data from similar studies to increase sample size and statistical power and achieve a more robust result.

In this meta-analysis, a total of 7 articles including 11 case and control studies were used to evaluate the association between *HLA-DQA1* gene rs2187668 polymorphism and iMN risk. In order to eliminate heterogeneity, we established strict inclusion and exclusion criteria, and only high-quality research which aim is the same can be included considering the consistency of the research object, exposure factors, etc. However, heterogeneities were still observed in the models except recessive model in our meta-analysis. The fixed-effect model was used in recessive model, and the result showed a significant association between rs2187668 genetic polymorphisms and iMN (Fig. 2). Because of heterogeneity, the random-effects model was adopted in other genetic models, which make the results relatively conservative, and the results also showed significant statistical differences

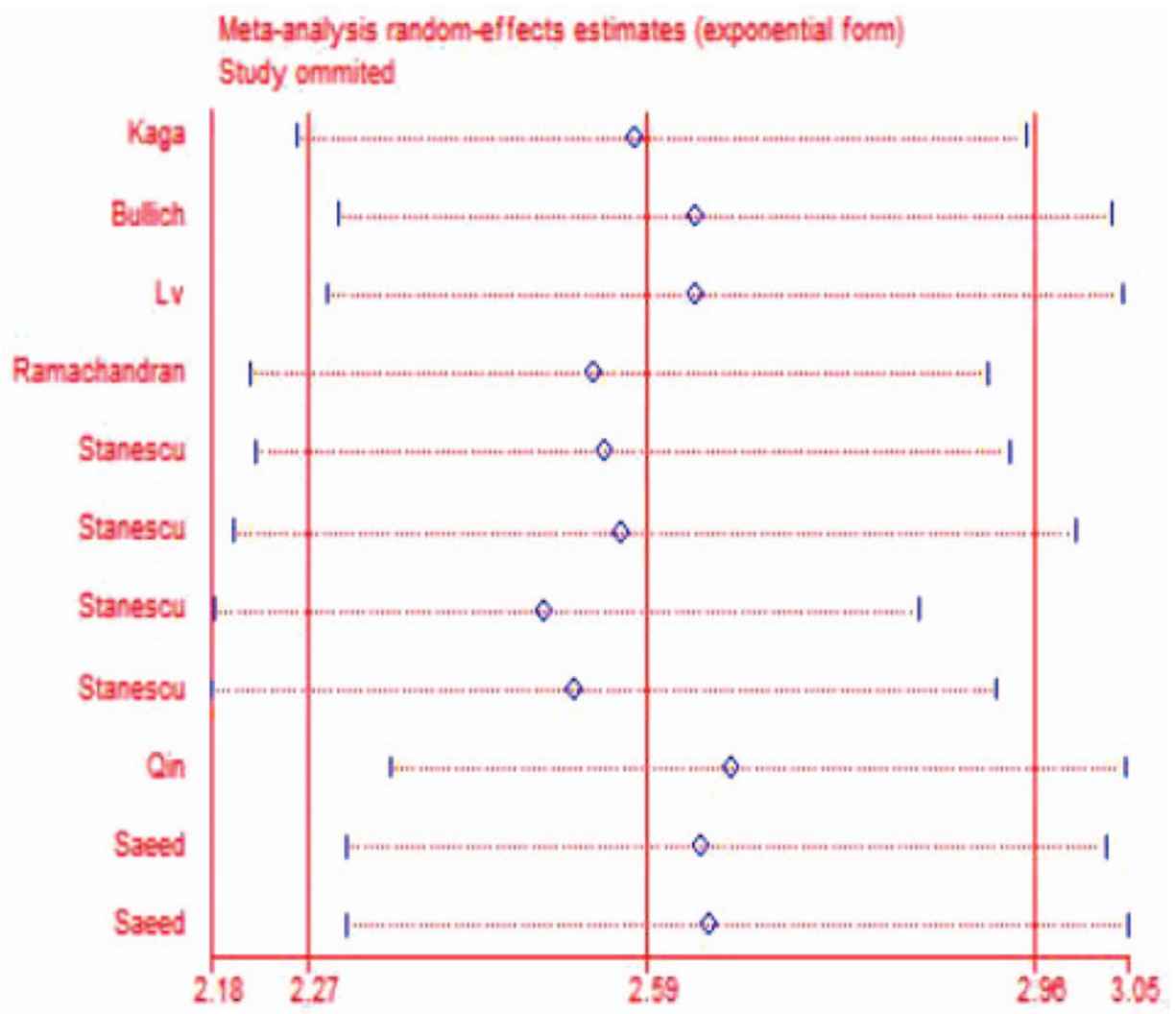

Figure 6. Sensitivity analysis of association between *HLA-DQA1* rs2187668 genetic variances and iMN. iMN = idiopathic membranous nephropathy.

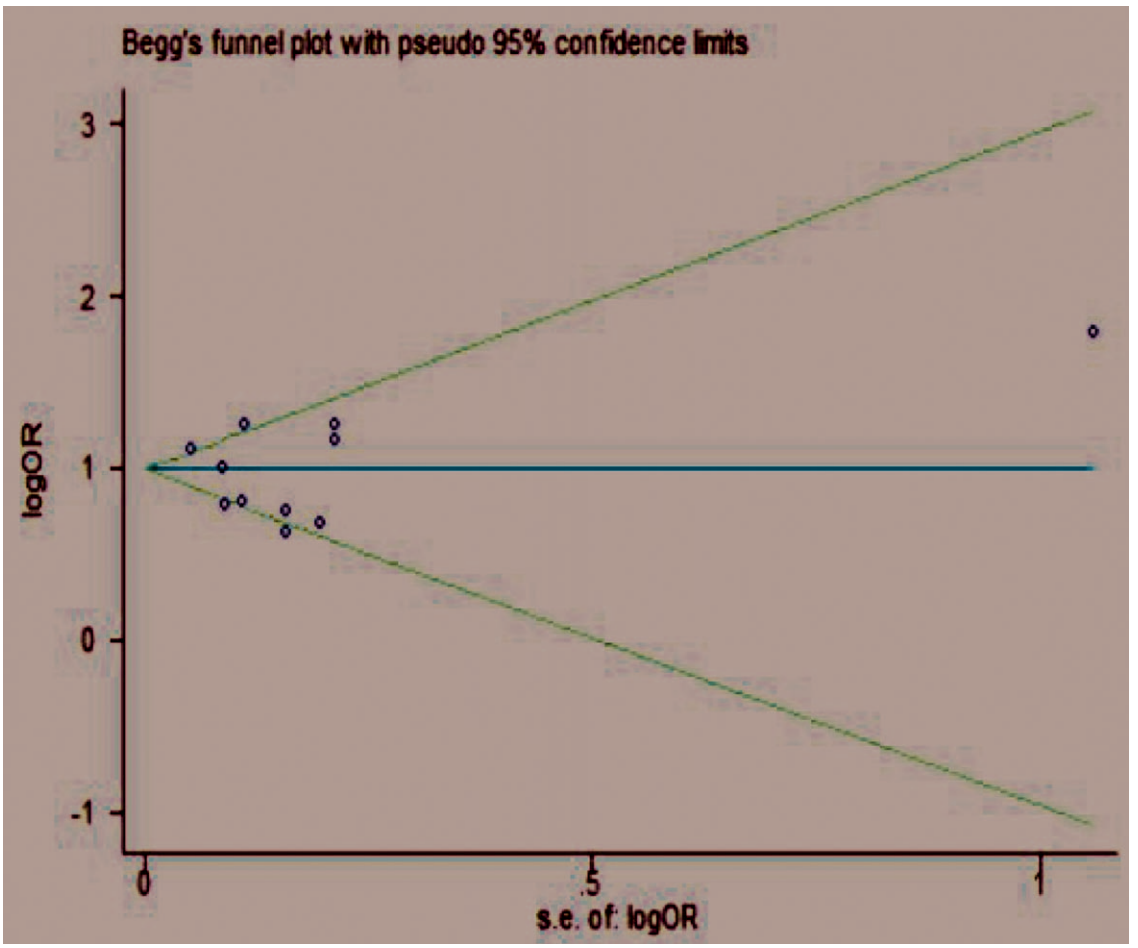

Figure 7. Assessment of publication bias in the analysis of the association between *HLA-DQA1*.rs2187668 gene polymorphism and iMN susceptibility. iMN= idiopathic membranous nephropathy.

(Fig. 1, Figs. 3–5). In addition, subgroup analysis was conducted to explore potential sources of heterogeneity. Considering that the polymorphism frequencies might differ among ethnic groups and control types, we performed a subgroup analysis by ethnicity and control source (Table 2). In the ethnicity-specific meta-analysis, a separate analysis was performed in Asian, European, Caucasian and American populations. The results demonstrated that the *HLA-DQA1* rs2187668 G/A polymorphism was associated with iMN risk in Asian, European and Caucasian. However, the result of American subgroup may not be reliable, since only one study was performed in American population. Moreover, the control source-specific meta-analysis was performed in hospital-based, population-based and not reported control sources. The results also showed that the *HLA-DQA1* rs2187668 G/A polymorphism was associated with iMN risk. After subgroup analysis by ethnicity and control source, heterogeneity still existed in the different genetic models, therefore, ethnic differences and control sources are not the cause of heterogeneity. iMN is a multifactorial disease, which interactions between many factors including age, gender, and so on.[21] But data for people of different age and gender were limited, and data were not available to perform subgroup analyses based on age or gender. Anyway, our result indicated that *HLA-DQA1* gene polymorphism was associated with iMN risk. And rs2187668 A allele was a risk factor for iMN. No publication bias was observed in our meta-analysis.

Some potential limitations of the present meta-analysis should be considered. First, all of the 11 studies included in this meta-analysis were based only on papers published in English, so studies in other languages did not attend this meta-analysis, which may cause selection bias. Second, there were only 2 studies with Caucasian populations and 1study with American populations, the exploration of moderator variables was limited by the low number of studies. Third, there was heterogeneity between studies of *HLA-DQA1* rs2187668 polymorphisms. Therefore, other risk factors are not well considered into analysis, such as age and gender which may affect the risk of iMN.

In conclusion, the results of our study indicate that *HLA-DQA1* rs2187668 polymorphism is associated with the susceptibility to iMN in Asians, Europeans, and Caucasians. Accordingly, the rs2187668 mutation was important in the iMN, and the intervention of this mutation might bring new therapeutic strategy for iMN. In the future, it is critical that further investigations with larger sample size, more ethnic groups and strict protocols to further validate the results of the current meta-analysis.

Author contributions

Conceptualization: Liping Bao, Xiaoyan Wu.
Data curation: Liping Bao, Jushuang Li.
Formal analysis: Jushuang Li.
Funding acquisition: Xiaoyan Wu.
Investigation: Liping Bao, Jushuang Li.
Methodology: Liping Bao.
Resources: Shuang Hu, Xiaoyan Wu.
Software: Shuang Hu.
Supervision: Xiaoyan Wu.
Validation: Shuang Hu.
Visualization: Shuang Hu.
Writing – original draft: Liping Bao.
Writing – review & editing: Xiaoyan Wu.

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